inhibitors is described in Nair, Lee & Hangauer 1995. The synthetic methodology used to develop a number of the src inhibitors is described in Lai et al., 1998.

Page 15, line 3, following Table I, please insert the following new paragraph:

The structure identified in Table 1 as Ac-Arg-Arg-Gly-Ala bonded to M_1-Ile-NH_2 is SEQ. ID. No. 3.

Page 17, line 5, following Table II, please insert the following new paragraph:

The structure identified in Table II as Ac-Ile-Tyr bonded to M_1-Gly-Glu-Phe-NH_2 is SEQ. ID. No. 2.

Page 19, line 10, following Table III, please insert the following new paragraph:

The structure identified in Table III as Ac-RRGXI-NH_2 is SEQ. ID. No. 4.

Please substitute the paragraph at page 19, line 10 to page 20, line 5 with the following new paragraph:

While testing these boronic acid-containing PKA inhibitors, the corresponding pentapeptide pseudosubstrate inhibitor **20** was included as an internal control while investigating time-dependent inhibition as shown in Table 3. Under Literature Mimetic assay conditions, and no preincubation, the initial results suggested that the shortest chain L-amino acid **21** was binding with the same affinity as the pseudosubstrate inhibitor **20** (i.e. K_i ca. 9 μM). As this side chain was increased in length (to **23** and then **24**) binding affinity appeared to decrease. When the stereochemistry of the unnatural amino acid was inverted from L in **21** to D in **22**, binding affinity appeared to increase 3-fold. This improvement in binding may occur as a result that the boronic acid OH in **21** is positioned at the same chain length as L-homoserine whereas the natural substrate, L-serine, has a one carbon shorter side chain. Modeling results with the PKA ternary structure indicated that the boronic acid OH can be retracted back somewhat by inverting the α-carbon stereochemistry from L in **21** to D in **22** and then repositioning the side chain to more closely mimic the positioning of the natural substrate L-serine OH adjacent to the catalytic residues (Asp-166 and Arg-168). The modeling results were subsequently supported by the finding that, upon incubation of PKA with these inhibitors for up to 4 hours without adding the competing peptide substrate

(Kemptamide: LRRASLG-NH_2) (SEQ. ID. No. 5), both 21 and 22 function as substrates with the D-diastereomer 22 being phosphorylated faster.

Page 21, line 4, before "The boronic acid" please insert the following new paragraph:

Phosphorylated Kemptamide is SEQ. ID. No. 6.

Please substitute the paragraph at page 22, line 13 to page 23, line 4 with the following new paragraph:

Since the src and IRTK structures are only used as qualitative guides in designing the non-peptide scaffolds and combinatorial libraries, the active sites along with two layers of surrounding residues were carved out from the native src and IRTK ternary structures, analogous to the previous PKA modeling studies. The IRTK:peptide:AMP-PNP ternary structure active site region was used as the template structure to guide the building of the src residue sequence 424-418 back onto the src structure using the comparative homology modeling technique (see Hutchins & Greer, 1991). These residues were disordered in the native src crystal structure and therefore not visible by x-ray. They were reintroduced because they help form the P+1 to P+3 binding sites for peptide substrates which are important for some of the modeling studies. The analogous residues in the IRTK ternary structure are seen by x-ray and directly interact with the bound peptide substrate. In fact, it is probably the presence of the bound peptide substrate which induces order in the positioning of this sequence so that it is visible by x-ray. The src pentapeptide substrate Ac-Ile-Tyr-Gly-Glu-Phe-NH_2 (SEQ. ID No. 1) (Nair et al., 1995) was then docked into the src active site again using the IRTK ternary structure as a template. Small adjustments were then manually made to partially clean up this complex, all of the hydrogen atoms were added, appropriate formal and partial charges (calculated via the Gasteiger Marsili method) were added, and then the entire complex was subjected to 300 iterations of molecular mechanics minimization using the Tripos force field, analogous to the previous PKA modeling procedure. A schematic representation of this modeled complex is given in Figure 5. Any inaccuracies in this src:peptide and the src:inhibitor models are accommodated by experimentally evaluating a range of side chains, the number and diversity of which is scaled roughly to the level of uncertainty for the structure of their particular binding region in the src model active site (see later), in a combinatorial fashion.